Vol 10

STIC-ILL

From: Canella, Karen
Sent: Wednesday, January 21, 2004 7:25 PM
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Art Unit 1642 Location Remsen 3A29 (office, I don't know my mail box address yet)

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Application Number PCT/US03/05042

1. Prostate Cancer and Prostatic Diseases:Mar 1999, 2(5-6):264-276

2. Protein Expression and Purification, 2000 Jun, 19(1):12-21

3. Proteomics, Oct 2001, 1(10):1264-1270

4. Clinical Chemistry, Oct 2001, 47(10):1901-1911

5. BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:370131 BIOSIS
DOCUMENT NUMBER: PREV200100370131
TITLE: Protein profiling of serum and seminal plasma using Ciphergen's SELDITM ProteinChip(R) technology for early detection of prostate cancer.
AUTHOR(S): Davis, John W. [Reprint author]; Adam, Bao-Ling [Reprint author]; Ward, Michael D. [Reprint author]; Clements, Mary Ann [Reprint author]; Cazares, Lisa H. [Reprint author]; Schellhammer, Paul F. [Reprint author]; Wright, George L., Jr. [Reprint author]; Dalmasso, Enrique; Feng, Ziding; Qu, Yinsheng; Yasui, Yutaka
CORPORATE SOURCE: Norfolk, VA, USA
SOURCE: Journal of Urology, (May, 2001) Vol. 165, No. 5 Supplement, pp. 203. print.
Meeting Info.: Annual Meeting of the American Urological Association, Inc. Anaheim, California, USA. June 02-07, 2001. American Urological Association, Inc.
CODEN: JOURAA. ISSN: 0022-5347.
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6. BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:270450 BIOSIS
DOCUMENT NUMBER: PREV200000270450
TITLE: Discovery of prostate cancer biomarkers from laser capture microdissected (LCM) cells using innovative ProteinChipTM SELDI mass spectroscopy.
AUTHOR(S): Cazares, L. H. [Reprint author]; Gong, L. [Reprint author]; Nasim, S.; Schellmammer, P. F. [Reprint author]; Wright, G. L., Jr. [Reprint author]
CORPORATE SOURCE: Eastern Virginia Med Sch, Norfolk, VA, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 851. print.
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 01-05, 2000.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
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treatment alternatives were offered to 58.9% (n: 181) in their stable phase (35 following medical treatment), while only 63 of them underwent surgery.

Conclusions: Our data suggest that, PD is a progressive in 33.3%, and stable in 60%, without any treatment in the acute phase. Penile deformities are disabling (greater than 30°) in 56.1% of cases, and risk factors for systemic vascular diseases are encountered in the majority. Since 58.9% of PD patients are candidates for surgery, close follow-up and detailed evaluation must be considered with a patient's-goal directed approach.

Prostate Cancer: Serum Markers (I)

Podium Session

Monday, June 4 2001 3:30-5:30 PM

839

SERUM PROTEIN ANALYSIS BY SURFACE ENHANCED LASER DESORPTIONAND IONIZATION TIME-OF-FLIGHT MASS SPECTROSCOPY (SELDI-TOF) COMBINED WITH ARTIFICIAL INTELLIGENCE-BASED PATTERN RECOGNITION: A NEW PARADIGM TO IMPROVE PROSTATE CANCER DETECTION

David K Ornstein, Chapel Hill, NC; Paul S Hackett, Ben A Hitt, Ali Ardekani, Cloud P Paweletz, W Marston Linehan, Michael R Emmert-Buck, Lance A Liotta, Emmanuel F Petricoin, Bethesda, MD; Alfredo Velasco, Christian Trucco, Santiago, Chile*

Introduction and Objectives: SELDI-TOF is a novel, extremely sensitive and rapid method to analyze complex mixtures of intact proteins and peptide fragments. Artificial intelligence based pattern recognition algorithms that evolve and learn through the acquisition of more data points are valuable tools to facilitate analysis of complex data sets such as the protein profiles generated by SELDI-TOF. In this study we utilize a novel pattern recognition algorithm called Knowledge Discovery Engine (KDE) to analyze serum protein profiles generated by SELDI-TOF.

Methods: Serum protein profiles were generated with the SELDI apparatus from Ciphergen Biosystems by applying 1 ul of serum to a hydrophobic interaction protein chip array. Profiles representing molecular masses of 1 - 20 kd were achieved by using alpha-cyano-4-hydroxy-cinnaminic acid for the matrix. The profiles were analyzed by KDE a pattern recognition algorithm developed by Correlogic Systems. Serum samples from 2 groups were obtained and analyzed. Group 2 consisted of 50 men: 25 with biopsy proven prostate cancer and PSA > 10.0 ng/ml, and 25 without cancer and PSA < 1.0 ng/ml. Group 2 comprised 43 men, 21 positive and 22 negative prostate biopsies. Group 1 was used to train the algorithm that was tested using samples from group 2.

Results: For group 1, all men were correctly identified as having cancer or benign prostates (100% accuracy). For group 2, 19/21 of men with cancer were correctly identified, as were 10/22 with negative biopsies. When 6 randomly selected cancer cases from group 2 were used to retrain the algorithm, the 15 remaining cancer patients were all correctly identified, as were 14/22 men with negative biopsies.

Conclusions: Analysis of serum proteins by SELDI-TOF and KDE discriminates men with prostate cancer from men with benign prostates regardless of total serum PSA level. Input of more data improves the accuracy of this novel diagnostic paradigm. Artificial intelligence based pattern recognition analysis of serum protein profiles generated by SELDI-TOF has the potential to improve detection of curable prostate cancer and reduce the cost and morbidity of PSA-based prostate cancer screening programs.

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PROTEIN PROFILING OF SERUM AND SEMINAL PLASMA USING CIPHERGEN'S SELDI™ PROTEINCHIP® TECHNOLOGY FOR EARLY DETECTION OF PROSTATE CANCER.

John W Davis, Bao-Ling Adam, Michael D Ward, Mary Ann Clements, Lisa H Cazares, Paul F Schellhammer, George L Wright Jr., Norfolk, VA; Enrique Dalmasso, Fremont, CA; Ziding Feng, Yinsheng Qu, Yutaka Yasui, Seattle, WA*

Introduction and Objectives: Serum PSA is an effective tool for early detection and post-treatment recurrence of prostate cancer (PCA), however specificity in the 4.0-10.0 ng./ml. range is only 25-30%. Because of the molecular and cellular heterogeneity of PCA, a combination or panel of biomarkers may improve the sensitivity and specificity of PCA screening. Ciphergen Biosystems, Inc., has developed a novel ProteinChip® mass spectrometry technology called SELDI™ (Surface Enhanced Laser Desorption/Ionization), which can rapidly detect known prostate biomarkers in raw samples of body fluids. We postulated that we could use this technology to identify multiple novel markers for PCA, and thus create fingerprint profiles of PCA versus BPH or normal.

Methods: Serum and seminal plasma samples were obtained from men with PCA (pre-treatment) and aged-matched normals. Samples were subjected to SELDI, and the resulting mass spectra analyzed by two computer software programs: Wavelet Transformation and a Binary-Marker combination approach. Initial analyses of the raw data were performed to determine diagnostic sensitivity/specificity.

Results: For serum, 167 PCA and 81 normal spectra were used as a training data set, and 30 PCA and 15 normal spectra were used as a test data set. Wavelet transformation gave a sensitivity/specificity of 93%/93% for detecting PCA. For Binary-Marker combination analysis, several protein peaks showed promise as diagnostic markers—especially when used in combination. The combination of 3 proteins gave a sensitivity/specificity of 60%/100%, the combination of 5 proteins 70%/100%, and the combination of 6 proteins 77%/93%. For seminal plasma, 24 PCA and 52 non-cancer (24 BPH + 28 normal) were used as a training set, and 15% of each group randomly used as a test set. The Binary-Marker combination method identified 8 potential diagnostic markers. Combination rules using 8 proteins resulted in a sensitivity / specificity of 87.5%/88.5% for PCA detection.

Conclusions: SELDI is a promising method of rapidly profiling proteins in serum and seminal plasma that may be developed into a rapid, high throughput clinical assay. Initial profiling of cancer versus age-matched normals showed sensitivity/specificity as high as 93% and 93%. Future comparisons will include PCA subgroups (local, advanced, hig vs low stage/grade), BPH, and correlation with serum PSA.

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PREOPERATIVE PLASMA LEVELS OF TRANSFORMING GROWTH FACTOR β1 STRONGLY PREDICT PROGRESSION IN PATIENTS UNDERGOING RADICAL PROSTATECTOMY

Shahrokh Shariat, Moshe Shalev, Andres Diaz-Menesses, Isaac Y Kim, Thomas M Wheeler, Kevin Slawin, Houston, TX; Michael W Kattan, New York, NY*

Introduction and Objectives: Elevated local and circulating levels of TGF-β1 have been associated with prostate cancer invasion and metastasis. We tested the hypothesis that preoperative plasma TGF-β1 levels would independently predict cancer stage and prognosis in patients undergoing radical prostatectomy.

Methods: The study group consisted of 120 consecutive patients who underwent radical prostatectomy (median follow-up of 53.8 months) for clinically localized prostate cancer. Preoperative platelet-poor plasma levels of TGF-β1 were measured and correlated with clinical and pathological parameters. TGF-β1 levels were also measured in 44 healthy men without any cancer, in 19 men with prostate cancer metastatic to regional lymph nodes, and in 10 men with prostate cancer metastatic to bone.

Results: Plasma TGF-β1 levels in patients with lymph node metastases (14.2 ±2.6 ng/mL) and bone metastases (15.5±2.4 ng/mL) were significantly higher than those in radical prostatectomy patients (5.2±1.3 ng/mL) and healthy subjects (4.5 ±1.2 ng/mL) (P values ≤ .001). Preoperative plasma TGF-β1 levels and biopsy Gleason score were both independent predictors of organ-confined disease (P=.006 and P=.006, respectively) and PSA progression (P ≤ .001 and P= .021, respectively). Within each pathological stage, patients who developed biochemical progression had significantly higher TGF-β1 levels than those who remained disease-free 48 months after surgery (P values ≤ .001). In patients who progressed, preoperative plasma TGF-β1 levels were significantly higher in those with presumed distant versus local-only failure (P= .019).

Conclusions: Plasma TGF-β1 levels are markedly elevated in men with prostate cancer metastatic to regional lymph nodes and bone. In men without overt metastases, the preoperative plasma TGF-β1 level is a strong predictor of biochemical progression after surgery, presumably because of an association with occult metastatic disease present at the time of radical prostatectomy.

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INSULIN-LIKE GROWTH FACTOR (IGF)-1 AND IGF-BINDING PROTEIN-3 IN THE DETECTION OF PROSTATE CANCER IN PATIENTS UNDERGOING PROSTATE BIOPSY

Armen Garo Aprikian, Hazem Ismail, Hassan Behlouli, Simon Tanguay, Louis Begin, Michael Pollak, Montreal, Canada*

Introduction and Objectives: Laboratory and epidemiological studies have provided evidence that high levels of circulating IGF-1 and low levels of IGFBP3 are associated with increased risk of prostate cancer development. However, the usefulness of serum IGF-1 or IGFBP3 in predicting the pathology results in men undergoing prostate biopsy is unclear. Our aim was to examine the relation of serum IGF-1 and IGFBP3 and the detection of prostate cancer.

Methods: 546 consecutive patients with either elevated serum PSA or abnormal digital rectal examination (DRE)who were referred for transrectal ultrasound and sextant prostate needle biopsy had blood drawn prior to biopsy, serum extracted

algorithm that was tested using samples from group 2.

Results: For group 1, all men were correctly identified as having cancer or benign prostates (100% accuracy). For group 2, 19/21 of men with cancer were correctly identified, as were 10/22 with negative biopsies. When 6 randomly selected cancer cases from group 2 were used to retrain the algorithm, the 15 remaining cancer patients were all correctly identified, as were 14/22 men with negative biopsies.

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840

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this technology to identify multiple novel markers for PCA, and thus create fingerprint profiles of PCA versus BPH or normal.

Methods: Serum and seminal plasma samples were obtained from men with PCA (pre-treatment) and aged-matched normals. Samples were subjected to SELDI, and the resulting mass spectra analyzed by two computer software programs: Wavelet Transformation and a Binary-Marker combination approach. Initial analyses of the raw data were performed to determine diagnostic sensitivity/specificity.

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